

Apocarotenals of Phenolic Carotenoids for Superior Antioxidant Activities<sup>†</sup>

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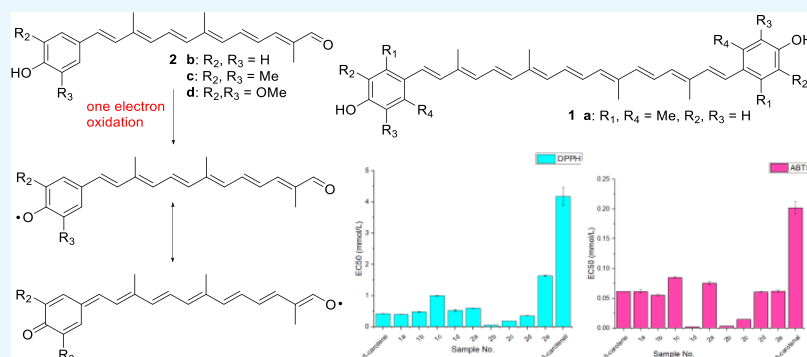
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**ABSTRACT:** A series of *para*-phenolic carotenes **1** with *ortho*- and *meta*-substitutions were respectively prepared utilizing the benzenesulfonyl protection method, which demonstrated the importance of the ring substituents on their effective conjugation, evaluated by their UV absorption values. The corresponding apo-12'-carotenals **2** were devised to improve the conjugation effect of the *para*-phenolic radical with the polyene chain by the conjugated aldehyde group. Apo-12'-carotenals **2b** and **2c** without *ortho*-substituents exhibited superior antioxidant activities to their corresponding symmetrical carotenes **1** as well as  $\beta$ -carotene and apo-12'- $\beta$ -carotenal in 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging assays.

## INTRODUCTION

Carotenoids are secondary metabolites produced by plants, bacteria, and microalgae, which are indispensable for energy production in photosynthesis. Carotenoids not only absorb visible light complementarily to chlorophyll but also transfer the harvested light energy to the photosynthetic reaction center to generate nicotinamide adenine dinucleotide phosphate (NADPH) and adenosine triphosphate (ATP).<sup>1</sup> Excessive energy during this process is dissipated by carotenoids to reversibly form transient cationic radicals, which would form stable adducts or decay to more stabilized oxidative degradation products such as apocarotenals.<sup>2</sup> Carotenoids react readily with any type of radicals, in which the main reaction profiles are adduct formation, electron transfer, and hydrogen abstraction.<sup>2</sup> The readiness to undergo such reactions makes carotenoids outstanding antioxidants, especially for scavenging reactive oxygen species in biological systems.<sup>3</sup>

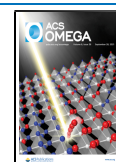
Isorenieratene is an unusual natural carotenoid containing polymethylated aromatic end groups.<sup>4</sup> The *para*-phenolic 3,3'-dihydroxyisorenieratene (DHIR, Figure 1), isolated first from *Streptomyces mediolani*,<sup>5</sup> was reported to exhibit superior antioxidant and photo-protective activities *in vitro* and *in vivo* assays.<sup>6</sup> The aromatic end groups would increase the

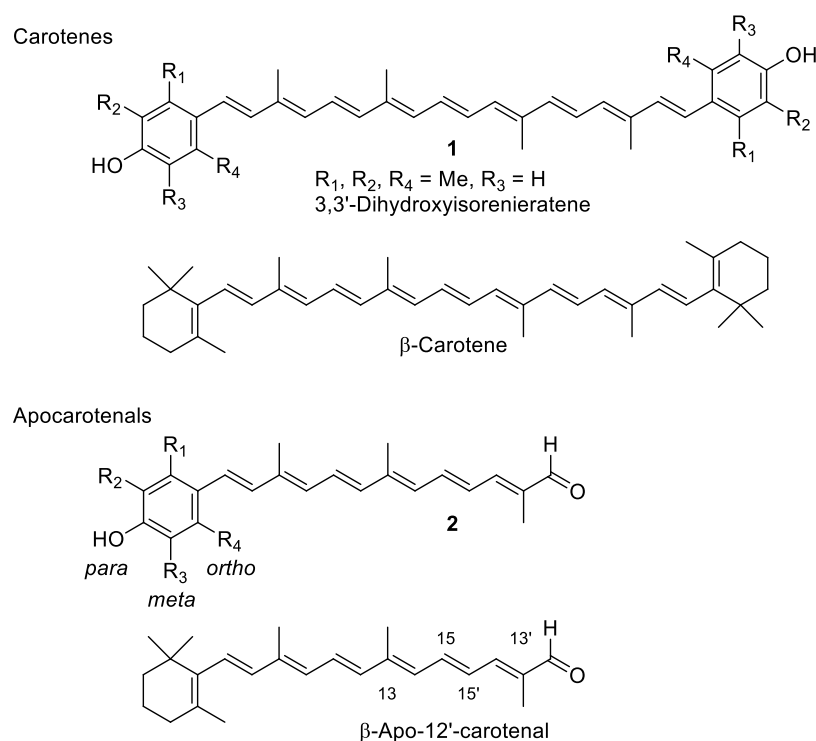
antioxidant ability independently or synergistically with the polyene chain. Methyl substituents in aromatic rings are reported to improve antioxidative property in the case of resveratrol,<sup>7</sup> but the *ortho*-methyl substituents in isorenieratene and DHIR adversely distort coplanarity of the benzene ring to the polyene chain.<sup>8</sup> Two-electron oxidation of the phenolic groups in DHIR, however, produces the quinoid structure, which would attain the full conjugation with the polyene chain to show a superior antioxidant activity.<sup>8</sup>

Apocarotenoids are the oxidative fragmentation products of the carotenoid polyene chain.<sup>9</sup> Even though the biological function and the enzymatic mechanisms are relatively well known for some apocarotenoids such as retinal,<sup>10</sup> bixin,<sup>11</sup> and abscisic acid,<sup>12</sup> those of the majority of apocarotenoids are still unclear.<sup>13</sup> They may be formed nonspecifically by eccentric cleavage from photo- or radical oxidation, but their prevalence in a biological system is well documented for the antioxidant,

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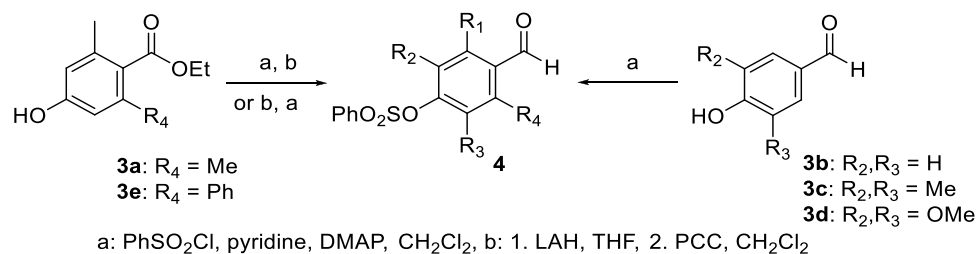
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**Figure 1.** Proposed carotenes **1** and apo-12'-carotenals **2** with phenol end group(s) for superior antioxidant activities.

### Scheme 1. Preparation of Protected 4-Hydroxybenzaldehydes **4** for the Phenol-Ending Carotenoids



stress signaling, and DNA-protective effects.<sup>14</sup> Searching for carotenoids of superior antioxidant activities, we were interested in the apocarotenals with a terminal benzene ring. It was hypothesized that apocarotenals with a *para*-phenol end group would exhibit superior antioxidant activity. Facile one-electron oxidation (or hydrogen radical abstraction) would produce a phenolic radical having the quinoid resonance structure, which is fully conjugated with the polyene aldehyde unit, whereas two-electron oxidation is required for DHIR to furnish the fully conjugated quinoid structure.

We first prepared *para*-phenolic carotenoids **1** with substitutions, respectively, at *ortho*- and *meta*-positions (derivatives of DHIR) to explain the importance of conjugation effect of the terminal phenol ring with the polyene chain (Figure 1). The corresponding apo-12'-carotenals **2** of *para*-phenolic carotenoids were devised to prove our hypothesis: increased conjugation effect of the phenolic radical with the conjugated polyene aldehyde group. The antioxidant activities for the above novel carotenoids were then measured by the standard radical scavenging assays of 1,1-diphenyl-2-picryl-hydrazyl (DPPH)<sup>15</sup> and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS).<sup>16</sup> Disappearance of the UV peaks from the above radicals by carotenoids through the formation of carotenoid cationic radicals can be correlated with

their antioxidant activities. The details of the syntheses and their antioxidant activities are herein described and compared with those of  $\beta$ -carotene and  $\beta$ -apo-12'-carotenal as references.

## RESULTS AND DISCUSSION

The syntheses of carotenes **1** and their apo-12'-carotenals **2** with diversely substituted *para*-phenol end group(s) were commenced from the preparation of the corresponding protected *para*-hydroxybenzaldehydes **4** (Scheme 1). The substituents at *ortho*- and *meta*-positions were selected among methyl, phenyl, and methoxy groups. *para*-Hydroxybenzaldehydes **3b** (without substitution), **3c** (*meta*-dimethyl), and **3d** (*meta*-dimethoxy) were commercially available. *ortho*-Substituted *para*-hydroxybenzoates **3a** (Me, Me) and **3e** (Me, Ph) were prepared according to our previously reported procedure.<sup>17</sup> Benzenesulfonyl protection for the *para*-hydroxyl group was utilized throughout the carotenoid syntheses, which was proven to survive the chain extension and olefination conditions and to be deprotected selectively in the presence of acid-sensitive polyene chain by KOH in *t*-BuOH.<sup>18</sup>

The *para*-hydroxybenzoate **3a** with *ortho*-dimethyl substituents was protected first by a benzenesulfonyl group (step a), and the ester group was transformed into a formyl group (step b) after reduction (LAH) and then oxidation (PCC).

The sterically hindered *para*-hydroxybenzoate **3e** with *ortho*-phenyl substituent required a harsh condition for the ester reduction (LAH in refluxing tetrahydrofuran (THF)), which accompanied undesirable desulfonylation. The sequence of the reaction steps was thus reversed (steps b then a) in this case to overcome the premature deprotection problem. The *para*-hydroxybenzaldehydes **3b–3d** were simply protected by a benzenesulfonyl group (step a) to produce the corresponding protected *para*-hydroxybenzaldehydes **4**.

Aldol condensation of the protected *para*-hydroxybenzaldehydes **4** with acetone in 1 M NaOH solution proceeded uneventfully to produce the chain-extended conjugated ketones **5**, from which the phosphonium salts **6** were prepared by the Grignard reaction with vinyl magnesium bromide, followed by HBr addition in the presence of PPh<sub>3</sub> at 0 °C. The Wittig olefination of **6** with 2,7-dimethylocta-2,4,6-trienal (**7**) was sequentially carried out first to produce protected apo-12'-carotenal **8** with a phenol end group under the mild condition at 0 °C utilizing NaHMDS as a base in THF. The all-*E* carotenals **8** were mostly obtained (based on <sup>1</sup>H NMR spectra) and further purified by trituration with Et<sub>2</sub>O.

The second Wittig reaction of **6** with the above-protected apo-12'-carotenal **8** required a harsh condition at 80 °C utilizing NaOMe as a base in MeOH/toluene to produce the protected phenol-ending carotenes **9**. Nevertheless, carotene **9e** with *ortho*-phenyl substituent was not produced presumably due to the steric reason. Expedient one-pot synthesis of carotene **9d** was demonstrated by the double Wadsworth–Emmons olefination of C<sub>20</sub> polyene diphosphonate **10** with protected hydroxybenzaldehyde **4d**.<sup>19</sup> Carotenoids **9** were mostly obtained as all-*E* form (based on <sup>1</sup>H NMR spectra) and further purified by recrystallization with a mixed solvent of MeOH and THF.

Deprotection of the benzenesulfonyl group from apo-12'-carotenals **8** and carotenes **9** was progressed smoothly using pulverized KOH in refluxing *t*-BuOH to afford the corresponding apo-12'-carotenals **2** and carotenes **1** with *para*-phenol end group(s), respectively. All-*E* configuration of the carotenoids was mostly maintained but deteriorated to 63% for apo-12'-carotenal **2b** (see high-performance liquid chromatography (HPLC) data in the Supporting Information). The reaction yield in each step of the above carotenoid syntheses is summarized in Table 1 (Scheme 2).

**Table 1. Yield of Each Compound in the Steps of Schemes 1 and 2**

compd.	4 (%)	5 (%)	6 (%)	8 (%)	2 (%)	9 (%)	1 (%)
a	33	79	99	56	52	53	72
b	73	95	25	63	96 <sup>a</sup>	35	35
c	98	88	68	21	19	37	67
d	95	87	57	30	45	26 <sup>b</sup>	78
e	47	62	68	21	13		

<sup>a</sup>All-*E* configuration was deteriorated after deprotection (all-*E*:*Z* = 1.7:1). <sup>b</sup>The reaction was performed by one-pot double olefination between C<sub>20</sub> diphosphonate **10** and **4d** (2 equiv).

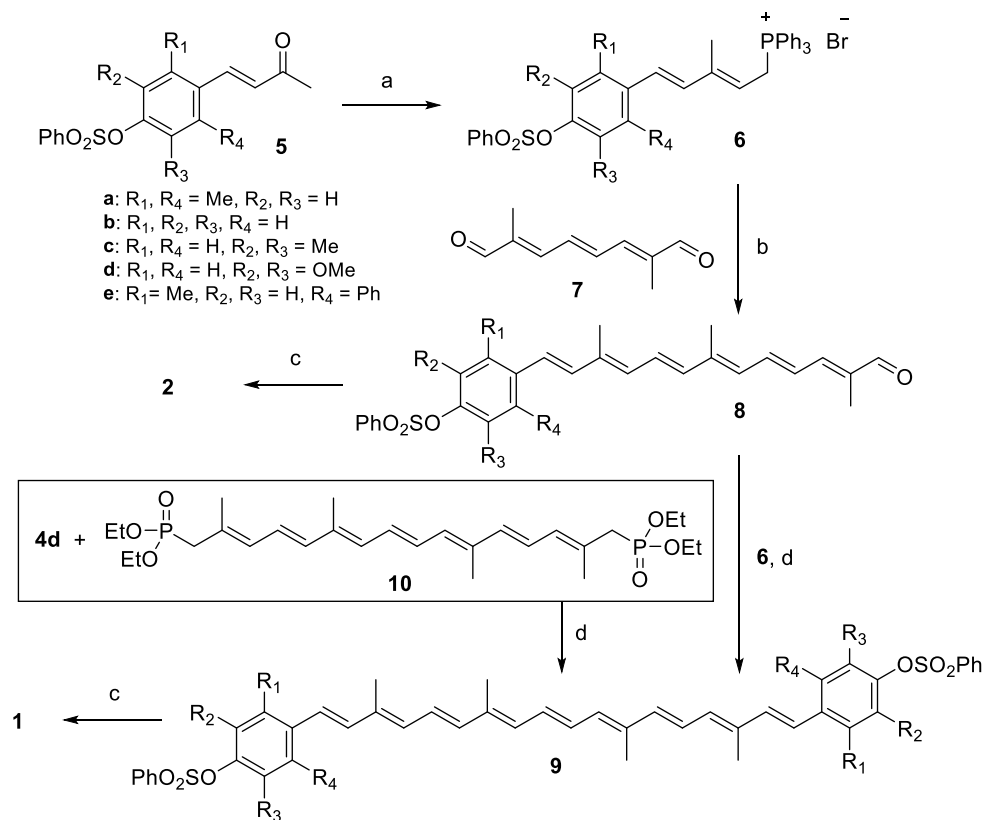
The structures of *ortho*- and *meta*-substituted carotenes **1** and their apo-12'-carotenals **2** with *para*-phenol end group(s) are listed in Figure 2 together with their UV absorption maxima ( $\lambda_{\max}$ ) in dimethyl sulfoxide (DMSO), which indicate the extent of  $\pi$ -conjugation between *para*-phenol group and the conjugated polyene chain. The phenol end group of

carotenoids **1a** and **2a** with *ortho*-dimethyl substitution would be deviated from coplanarity to the conjugated polyene chain due to the steric hindrance, thereby lowest UV absorption values (by ~20 nm) were observed in each series. *para*-Phenolic carotenes **1** with no other substitution (**1b**) and *meta*-substitution (**1c** and **1d**) showed a very specific UV absorption value at 501 ± 2 nm, which explained the effective conjugation of the *para*-phenol group to the polyene chain. Similarly, the highest UV absorption value (465 nm) was observed for *para*-phenolic apo-12'-carotenals **2b** with no other substitution and **2c** with *meta*-dimethyl substitution in the series, whereas a little lower value (452 nm) measured for **2d** with *meta*-dimethoxy substitution was presumably due to an intramolecular hydrogen bonding of phenol with the neighboring methoxy group, which might slightly reduce the conjugation effect. The  $\lambda_{\max}$  difference between **2a** and **2e** can be ascribed to the auxochrome effect by the *ortho*-phenyl group in **2e**, which exhibited a redshift by 6 nm.

Antioxidant activities of carotenoids **1** and **2** were measured by DPPH and ABTS radical scavenging assays. Disappearance of the UV absorption peak for relatively stable DPPH radical at 580 nm (instead of interfered 510 nm wavelength)<sup>15b</sup> by carotenoids was monitored to obtain EC<sub>50</sub> values, which can be explained by quenching with hydrogen atom (H<sup>•</sup>) of phenol as well as a single  $\pi$ -electron from the polyene chain. ABTS cationic radical, which was in situ generated from the oxidation by potassium persulfate and exhibits the UV absorption maximum wavelength at 734 nm, can be quenched mainly by a single  $\pi$ -electron of the carotenoids. DPPH assay would thus be more suitable to incorporate the effect of phenol group in carotenoids with the *para*-phenol end group(s). The EC<sub>50</sub> values of DPPH and ABTS assays for carotenoids **1** and **2** were measured quadruple and their mean and standard deviation values are listed in Table 2, which were compared with those of  $\beta$ -carotene and  $\beta$ -apo-12'-carotenal as references.

The effects of the end groups in natural carotenoids on the antioxidant activity were studied theoretically and experimentally.<sup>20</sup> The polarity of the terminal group affected the radical scavenging ability of natural carotenoids: carotenoids (lycopene and  $\beta$ -carotene) > hydroxy-carotenoids (zeaxanthin and lutein) > keto-carotenoids (astaxanthin and canthaxanthin) in phenoxy radical<sup>21</sup> and ABTS cationic radical scavenging experiments.<sup>22</sup> The effective conjugation length is also important in carotenoids' antioxidant activity,<sup>23</sup> and shorter  $\beta$ -apo-8'-carotenal was reported to exhibit poorer radical scavenging activity than  $\beta$ -carotene,<sup>21</sup> which was also demonstrated by our referenced EC<sub>50</sub> values of  $\beta$ -carotene and  $\beta$ -apo-12'-carotenal in Table 2.

Considering the above effects, the results in Table 2 are astonishing in that (1) apo-12'-carotenals **2** with a *para*-phenol end group are superior to the corresponding carotenes **1** in DPPH radical scavenging (except the sterically hindered *ortho*-substitution case a) and (2) polar hydroxy-carotenoids **1** are generally better than  $\beta$ -carotene in ABTS radical scavenging. In fact, apo-12'-carotenals **2b** and **2c** without *ortho*-substitution are superior in radical scavenging activities presumably by the effective conjugation of coplanar phenolic radical with the conjugated polyene aldehyde, which proves our hypothesis in this study. On the other hand, the radical scavenging abilities of carotenoids **1** are not correlated with the phenolic substitution patterns (or the UV absorption values). It could be explained that the resonance stabilized coplanar phenolic radicals of **2b** and **2c** without *ortho*-substitution were readily

Scheme 2. Synthetic Routes for the Phenol-Ending Carotenes **1** and Apo-12'-carotenals **2**

a: 1. vinyl magnesium bromide, THF, -78 °C, 2. PPh<sub>3</sub>, HBr, THF, b: NaHMDS, THF, 0 °C, c: KOH, *t*-BuOH, toluene, reflux, d: NaOMe, MeOH, toluene, 80 °C, 1 d.

formed by facile one-electron oxidation, whereas two-electron oxidations would be necessary for carotenes **1** with *para*-phenol end groups to afford the fully conjugated coplanar quinoid structures.<sup>8</sup> Density functional theory (DFT) calculation (Supporting Information) also supports the above results in that the singly occupied molecular orbital (SOMO) energy of **2b** radical is lower by 6.41 kcal/mol than that of **1b** radical. The energy gain by an electron transition from the highest occupied molecular orbital (HOMO) to the SOMO level is larger for **2b** (3.13 kcal/mol) than that for **1b** (2.72 kcal/mol). The strong ABTS radical scavenging activity of **1d** can be ascribed to the charge-transfer complex formation of the electron-rich phenol rings with ABTS, which can be explained by prompt appearance of reddish-black color.

## CONCLUSIONS

*para*-Phenolic carotenoids **1** and their apo-12'-carotenals **2** with ortho- and meta-substitutions were, respectively, prepared from the corresponding *para*-hydroxybenzaldehydes utilizing the benzenesulfonyl protection method. UV absorption values by the  $\pi$ -electronic transition of carotenoids **1** and **2** explained the effective conjugation length between the *para*-phenol group and the polyene chain by coplanarity, which was negatively affected by the sterically hindered ortho-substituents. Antioxidant activities of carotenoids **1** and **2**, measured by DPPH and ABTS radical scavenging assays, indicated somewhat different trends in the stability of carotenoid radicals. The *para*-phenolic radicals of apo-12'-carotenals **2** with no ortho-substitution were effectively conjugated with the polyene

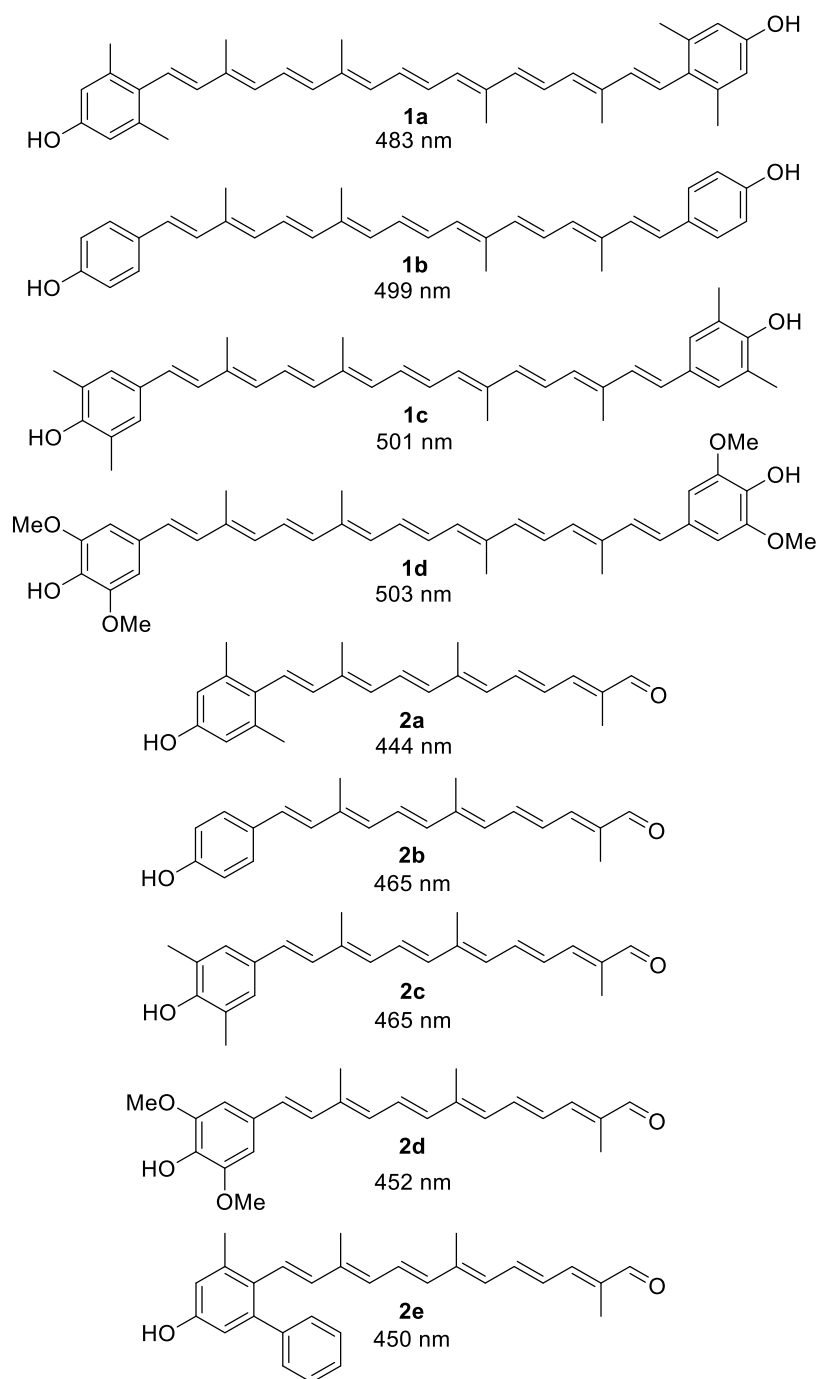
aldehyde unit, which were even better stabilized than those of the corresponding carotenes **1**. Superior radical scavenging activities were observed for *para*-phenolic apo-12'-carotenals **2b** and **2c** with no ortho-substitution in DPPH and ABTS assays.

## EXPERIMENTAL SECTION

**General Experimental.** Reactions were generally performed in a well-dried flask under argon atmosphere unless noted otherwise. Solvents for extraction and chromatography were of reagent grade and used as received. The column chromatography was performed with silica gel 60 (70–230 mesh) using a mixture of EtOAc/hexane as an eluent. <sup>1</sup>H- and <sup>13</sup>C NMR spectra were, respectively, recorded on 400 and 100 MHz NMR spectrometers in deuterated chloroform (CDCl<sub>3</sub>) with tetramethylsilane (TMS) as an internal reference unless noted otherwise. The syntheses of carotenes **1** and apo-12'-carotenals **2** were described for the Series I of 2,6-dimethyl-4-hydroxyphenyl end group (a). Only the analytical data were given for the other Series II–V (b–e).

2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 1,1-diphenyl-2-picryl-hydrazyl (DPPH), and potassium persulfate were purchased from Sigma-Aldrich, Inc.  $\beta$ -Carotene<sup>24</sup> and  $\beta$ -apo-12'-carotenal<sup>25</sup> used for ABTS and DPPH assays were freshly prepared according to the literature procedure. 2,7-Dimethyl-2,4,6-octatriendial (**7**) was obtained from BASF as a generous gift.

**DPPH Assay.**<sup>15</sup> DPPH is a stable free radical with UV absorption maximum at 517 nm. Because of the interference of



**Figure 2.** Carotenoids **1** and apo-12'-carotenals **2** with *para*-phenol end group(s) and their UV absorption values ( $\lambda_{\max}$ ) in DMSO.

carotenoids at around 510 nm, the depletion of DPPH radical by carotenoid scavenging was measured at 580 nm.<sup>15b</sup> A  $6.31 \times 10^{-2}$  mM stock solution of DPPH in methanol was prepared, and it was diluted 1/100 with MeOH right before use. A  $6.31 \times 10^{-5}$  mM DPPH solution in MeOH (0.2 mL) was added to various carotenoid sample solutions (0.05 mL) in THF/DMSO (1:1). Keeping the mixture in the dark at room temperature for 2 h, an aliquot (0.05 mL) was placed in a 384-cell cuvette, in which the absorbance was determined at 580 nm by a UV-vis microplate spectrophotometer (Multiskan GO by Thermo Scientific Co.) in fourfold analyses.

**ABTS Assay.**<sup>16</sup> The ABTS cationic radical was freshly prepared by treating an aqueous solution of ABTS

diammonium salt (2.5 mL, 7.4 mM) with an aqueous solution of potassium persulfate (2.5 mL, 2.6 mM). The mixture was kept in the dark at room temperature for 12 h and then diluted with methanol (about 1/50 of volume) until its absorbance value became  $0.70 \pm 0.02$  at 734 nm. Typically, fresh ABTS<sup>•+</sup> stock solution (2 mL) was added to various carotenoid sample solutions (0.05 mL) in THF/DMSO (1:1). Keeping the mixture in the dark at room temperature for 2 h, an aliquot (0.05 mL) was placed in a 384-cell cuvette, in which the absorbance was determined at 734 nm by a UV-vis microplate spectrophotometer (Multiskan GO by Thermo Scientific Co.) in fourfold analyses.

Table 2. EC<sub>50</sub> of Carotenoids in Figure 2 for DPPH and ABTS Radical Scavenging Assays

rank	DPPH		ABTS	
	compound	EC <sub>50</sub> (mM)	compound	EC <sub>50</sub> (mM)
1	2b	0.0562 ± 0.0009	1d	0.0019 ± 1.1E-5
2	2c	0.1840 ± 0.0019	2b	0.0030 ± 6.9E-5
3	2d	0.3550 ± 0.0025	2c	0.0144 ± 8.8E-5
4	1a	0.3954 ± 0.0036	1b	0.0552 ± 0.0014
5	<u>β-carotene</u>	0.4216 ± 0.0028	2d	0.0606 ± 0.0007
6	1b	0.4828 ± 0.0056	1a	0.0614 ± 0.0028
7	1d	0.5234 ± 0.0286	<u>β-carotene</u>	0.0614 ± 0.0002
8	2a	0.5987 ± 0.0028	2e	0.0616 ± 0.0021
9	1c	0.9966 ± 0.0111	2a	0.0752 ± 0.0032
10	2e	1.6313 ± 0.0182	1c	0.0849 ± 0.0010
11	<u>β-12'-carotenal</u>	4.1747 ± 0.2845	<u>β-12'-carotenal</u>	0.2017 ± 0.0101

**Series 1 (a).** Ethyl 2,6-Dimethyl-4-((phenylsulfonyl)oxy)benzoate. To a stirred solution of ethyl 4-hydroxy-2,6-dimethylbenzoate (3a)<sup>17</sup> (5.61 g, 28.87 mmol) and benzene-sulfonyl chloride (6.12 g, 34.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were added pyridine (4.57 g, 57.74 mmol) and dimethylamino-pyridine (106 mg, 0.87 mmol). The mixture was stirred at room temperature under argon atmosphere for 1 day, diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with 1 M HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product (9.95 g) as a brown oil. The crude product was purified by SiO<sub>2</sub> flash column chromatography (eluent 10–35% EtOAc/hexane) to give the title compound (5.43 g, 16.24 mmol) in 56% yield as a light yellow solid. Data: R<sub>f</sub> = 0.31 (1:4 EtOAc/hexane); m.p. = 75–76 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.37 (t, J = 7.2 Hz, 3H), 2.24 (s, 6H), 4.38 (q, J = 7.2 Hz, 2H), 6.67 (s, 2H), 7.51–7.59 (m, 2H), 7.65–7.71 (m, 1H), 7.83–7.90 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.1, 19.5, 61.1, 121.0, 128.3, 129.0, 132.9, 134.2, 135.2, 137.0, 149.3, 168.8 ppm; IR (KBr) 2982, 1722, 1595, 1469, 1446, 1372, 1260, 1185, 1133, 1088, 1021, 962, 872, 783, 753, 723, 686, 596, 574 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>17</sub>H<sub>18</sub>O<sub>5</sub>S 334.0875, found 334.0874.

**4-Formyl-3,5-dimethylphenyl Benzenesulfonate (4a).** To a stirred solution of ethyl 2,6-dimethyl-4-((phenylsulfonyl)oxy)benzoate (5.48 g, 16.39 mmol) in THF (55 mL) was added LAH (622 mg, 16.39 mmol) at 0 °C. The mixture was slowly warmed to and stirred at room temperature for 15 h. The mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with 1 M HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude benzylic alcohol (4.72 g, 16.13 mmol) as a yellow oil (R<sub>f</sub> = 0.25, 2:3 EtOAc/hexane). Data: IR (KBr) 3422, 2960, 2922, 1722, 1595, 1476, 1446, 1372, 1275, 1185, 1126, 1096, 1021, 962, 872, 820, 753, 731, 686, 589, 574 cm<sup>-1</sup>.

The crude benzylic alcohol (4.72 g, 16.13 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (35 mL), and silica gel (5.0 g) and PCC (4.17 g, 19.36 mmol) were added. The mixture was stirred at room temperature for 14 h under argon atmosphere and filtered through a sintered glass funnel under reduced pressure. The filtrate was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with NaHCO<sub>3</sub> solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product (3.79 g) as a brown oil, which was purified by SiO<sub>2</sub> flash column chromatography to give benzaldehyde 4a (2.74 g, 9.45 mmol) in 59% yield as a yellow oil (R<sub>f</sub> = 0.26, 1:4 EtOAc/hexane). Data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.53 (s, 6H), 6.75 (s, 2H), 7.53–7.60 (m, 2H), 7.67–7.73 (m, 1H), 7.85–7.91 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 20.4, 122.8, 128.3, 129.2, 131.0, 134.4, 135.1, 143.5,

151.6, 192.1 ppm; IR (KBr) 3066, 3032, 2978, 2932, 2870, 2770, 1694, 1591, 1450, 1373, 1276, 1193, 1128, 1095, 1026, 966, 878, 818, 748, 711, 688 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>O<sub>4</sub>S 290.0613, found 290.0609.

**(E)-3,5-Dimethyl-4-(3-oxobut-1-en-1-yl)phenyl Benzenesulfonate (5a).** To a stirred solution of benzaldehyde 4a (2.39 g, 8.21 mmol) in acetone (10 mL) was added 1 M NaOH solution (20 mL). The mixture was stirred at room temperature for 1 day, acidified with 1 M HCl (30 mL), and extracted with Et<sub>2</sub>O. The aqueous layer was extracted again with EtOAc, and the combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product (2.87 g) as a yellow oil, which was purified by SiO<sub>2</sub> flash column chromatography (eluent 15–50% EtOAc/hexane) to give conjugated enone 5a (2.16 g, 6.52 mmol) in 79% yield as an off-white solid. Data: R<sub>f</sub> = 0.13 (1:4 EtOAc/hexane); m.p. = 74–76 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.23 (s, 6H), 2.36 (s, 3H), 6.27 (d, J = 16.4 Hz, 1H), 6.69 (s, 2H), 7.51–7.58 (m, 2H), 7.52 (d, J = 16.4 Hz, 1H), 7.64–7.70 (m, 1H), 7.82–7.88 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 20.7, 27.2, 121.3, 128.0, 128.9, 132.7, 133.1, 134.0, 135.0, 138.2, 140.1, 148.4, 197.8 ppm; IR (KBr) 3064, 2967, 1692, 1670, 1588, 1476, 1446, 1364, 1152, 1185, 1126, 1096, 1021, 962, 880, 820, 753, 716, 686, 596, 567 cm<sup>-1</sup>; HRMS (CI) calcd for C<sub>18</sub>H<sub>19</sub>O<sub>4</sub>S 331.1004, found 331.0997.

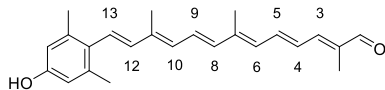
**((2E,4E)-5-(2,6-Dimethyl-4-((phenylsulfonyl)oxy)phenyl)-3-methylpenta-2,4-dien-1-yl)triphenylphosphonium Bromide (6a).** To a stirred solution of conjugated enone 5a (4.55 g, 13.77 mmol) in THF (25 mL) at –78 °C under argon atmosphere was added 1 M THF solution of vinyl magnesium bromide (21 mL, 21.0 mmol). The mixture was stirred at that temperature for 3 h and quenched with NH<sub>4</sub>Cl solution. The reaction mixture was diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O. The aqueous layer was extracted again with EtOAc. The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude vinylic alcohol product (5.13 g) as a yellow oil. Data: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.48 (s, 3H), 2.18 (s, 6H), 5.13 (d, J = 10.8 Hz, 1H), 5.30 (s, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.76 (d, J = 16.0 Hz, 1H), 6.04 (dd, J = 17.2, 10.8 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 6.65 (s, 2H), 7.50–7.58 (m, 2H), 7.64–7.70 (m, 1H), 7.84–7.90 (m, 2H) ppm.

To a stirred solution of the above crude alcohol (5.13 g) in THF (50 mL) at 0 °C were added PPh<sub>3</sub> and 48% HBr aqueous solution. The reaction mixture was stirred at 0 °C for 2 h and slowly warmed to and stirred at room temperature for 10 h. Most of solvent was removed under reduced pressure to give

the crude product (10.39 g) as a light yellow solid. The crude product was purified by SiO<sub>2</sub> flash column chromatography (eluent: 50% EtOAc/hexane 350 mL, CH<sub>2</sub>Cl<sub>2</sub> 250 mL, and then MeOH 300 mL) to give the Wittig salt **6a** (9.36 g, 13.69 mmol) in 99% yield as an ivory solid. Data: m.p. = 66–68 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.51 (d, *J* = 2.8 Hz, 3H), 2.13 (s, 6H), 5.01 (dd, *J* = 15.2, 8.0 Hz, 2H), 5.45 (dt, *J*<sub>d</sub> = 6.8, *J*<sub>t</sub> = 8.0 Hz, 1H), 6.11 (d, *J* = 16.4 Hz, 1H), 6.33 (d, *J* = 16.4 Hz, 1H), 6.63 (s, 2H), 7.43–7.95 (m, 20H) ppm; IR (KBr) 2924, 1589, 1481, 1435, 1373, 1188, 1119, 1018, 964, 910, 748, 687 cm<sup>-1</sup>; HRMS (FAB) calcd for C<sub>38</sub>H<sub>36</sub>O<sub>3</sub>PS 603.2123, found 603.2128.

**3,5-Dimethyl-4-((1E,3E,5E,7E,9E,11E)-3,7,12-trimethyl-13-oxotrideca-1,3,5,7,9,11-hexaen-1-yl)phenyl Benzenesulfonate (8a)**. To a stirred suspension of the above Wittig salt **6a** (3.00 g, 4.39 mmol, 3 equiv) in THF (30 mL) at 0 °C under argon atmosphere was added 1 M THF solution of NaHMDS (5.0 mL, 5.0 mmol). The resulting mixture turned to dark red and was stirred at 0 °C for 25 min, and a solution of C<sub>10</sub> dialdehyde **7** (240 mg, 1.46 mmol) in THF (10 mL) was added. The reaction mixture was stirred at that temperature for 2 h and slowly warmed to and stirred at room temperature for 9 h. The mixture was diluted with Et<sub>2</sub>O and washed with NH<sub>4</sub>Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give the crude product (3.53 g), which was purified by SiO<sub>2</sub> flash column chromatography (eluent 15–50% EtOAc/hexane) to give the mono-coupled aldehyde **8a** (401 mg, 0.82 mmol) in 56% yield as a red solid. Data: *R*<sub>f</sub> = 0.18 (1:4 EtOAc/hexane); m.p. = 78–80 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.89 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.23 (s, 6H), 6.24 (d, *J* = 11.6 Hz, 1H), 6.32 (d, *J* = 11.6 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 6.42 (d, *J* = 15.2 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.67 (s, 2H), 6.70 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.80 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.96 (d, *J* = 11.6 Hz, 1H), 7.03 (dd, *J* = 15.2, 11.6 Hz, 1H), 7.51–7.60 (m, 2H), 7.64–7.72 (m, 1H), 7.84–7.93 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 9.5, 12.7, 13.0, 21.1, 121.2, 125.2, 127.1, 127.7, 128.4, 129.0, 131.5, 132.4, 134.0, 135.7, 136.2, 136.8, 137.0, 137.5, 137.6, 137.8, 139.2, 141.4, 147.4, 148.8, 194.4 ppm; UV (CHCl<sub>3</sub>, *c* = 2.98 × 10<sup>-6</sup>) λ<sub>max</sub> (ε) = 430 (231 088) nm; IR (KBr) 2915, 2728, 1662, 1588, 1469, 1446, 1372, 1275, 1185, 1126, 1096, 1014, 962, 872, 820, 745, 686, 663, 589, 567, 544 cm<sup>-1</sup>; HRMS (FAB) calcd for C<sub>30</sub>H<sub>32</sub>O<sub>4</sub>S 488.2021, found 488.2015.

**(2E,4E,6E,8E,10E,12E)-13-(4-Hydroxy-2,6-dimethylphenyl)-2,7,11-trimethyltrideca-2,4,6,8,10,12-hexaenal (2a)**.



To a stirred solution of sulfone-protected apo-carotene **8a** (0.30 g, 0.61 mmol) in *t*-BuOH/toluene (6 mL/24 mL) was added pulverized KOH (870 mg, 15.5 mmol). The mixture was then heated to reflux for 20 min and cooled to room temperature. Most of solvent was removed under reduced pressure. The crude product was dissolved in EtOAc, washed with 1 M HCl solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by SiO<sub>2</sub> flash column chromatography to give **2a** (111 mg, 0.32 mmol) in 52% yield as a red solid (trituted with Et<sub>2</sub>O). Data: *R*<sub>f</sub> = 0.29 (hexane/acetone 3:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.89 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.29 (s,

6H), 6.23 (d, *J* = 12.0 Hz, 1H; H-6), 6.31 (d, *J* = 11.6 Hz, 1H; H-10), 6.34 (d, *J* = 16.0 Hz, 1H; H-12), 6.41 (d, *J* = 14.8 Hz, 1H; H-8), 6.56 (s, 2H), 6.60 (d, *J* = 16.0 Hz, 1H; H-13), 6.69 (dd, *J* = 14.8, 12.0 Hz, 1H; H-5), 6.83 (dd, *J* = 14.8, 11.6 Hz, 1H; H-9), 6.97 (d, *J* = 11.6 Hz, 1H; H-3), 7.04 (dd, *J* = 14.8, 11.6 Hz, 1H; H-4), 9.46 (s, 1H) ppm; UV (DMSO, *c* = 6.38 × 10<sup>-6</sup>) λ<sub>max</sub> (ε) = 444 (60 843) nm; IR (KBr) 3358, 2956, 2934, 2853, 1663, 1606, 1544, 1448, 1378, 1309, 1262, 1215, 1187, 1150, 1029, 968, 910, 801, 761, 736, 650 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>24</sub>H<sub>28</sub>O<sub>2</sub>+Na 371.1982, found 371.1985. The <sup>13</sup>C NMR spectrum could not be obtained due to lower solubility of **2a** in any solvent.

**((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(3,5-dimethyl-4,1-phenylene) Dibenzenesulfonate (9a)**. The mixture of the mono-coupled aldehyde **8a** (600 mg, 1.30 mmol) and the above Wittig salt **6a** (2.57 g, 3.76 mmol, 2.7 equiv) in toluene (30 mL) and MeOH (30 mL) was treated with NaOMe (406 mg, 7.52 mmol). The mixture was then heated to 80 °C for 1 day and cooled to room temperature. Most of solvent was removed under reduced pressure. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with NH<sub>4</sub>Cl solution, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give the crude product (2.89 g) as a red oil, which was purified by SiO<sub>2</sub> flash column chromatography (eluent 15–60% EtOAc/hexane) to give carotene **9a** (560 mg, 0.69 mmol) in 53% yield as a red solid (*R*<sub>f</sub> = 0.17, 1:4 EtOAc/hexane). The analytical sample was prepared by recrystallization with MeOH and THF. Data: m.p. = 92–94 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.97 (s, 6H), 2.03 (s, 6H), 2.21 (s, 12H), 6.21 (d, *J* = 11.2 Hz, 2H), 6.23–6.31 (m, 2H), 6.30 (d, *J* = 16.4 Hz, 2H), 6.38 (d, *J* = 14.8 Hz, 2H), 6.44 (d, *J* = 16.1 Hz, 2H), 6.59–6.67 (m, 2H), 6.64 (s, 4H), 6.65 (dd, *J* = 14.8, 11.2 Hz, 2H), 7.50–7.57 (m, 4H), 7.64–7.70 (m, 2H), 7.84–7.90 (m, 4H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 12.7, 12.8, 21.2, 121.2, 124.2, 124.7, 128.5, 129.0, 130.3, 132.9, 133.1, 134.0, 135.1, 135.7, 136.4, 136.5, 137.8, 138.4, 139.4, 147.3 ppm; UV (CHCl<sub>3</sub>, *c* = 1.88 × 10<sup>-6</sup>) λ<sub>max</sub> (ε) = 465 (275 124) nm; IR (KBr) 3040, 2986, 2916, 2862, 1582, 1466, 1450, 1373, 1273, 1188, 1126, 1096, 1018, 972, 910, 880, 826, 772, 733, 679, 648, 617, 579 cm<sup>-1</sup>; HRMS (FAB) calcd for C<sub>50</sub>H<sub>52</sub>O<sub>6</sub>S<sub>2</sub> 812.3205, found 812.3205.

**4,4'-((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(3,5-dimethylphenol) (1a)**. To a stirred solution of carotene (179 mg, 0.22 mmol) in toluene (20 mL) were added pulverized KOH (300 mg, 5.35 mmol, 25 equiv) and *t*-BuOH (5 mL). The mixture was heated to reflux for 1.5 h and cooled to room temperature. Most of solvent was removed under reduced pressure. The crude product was dissolved in EtOAc, washed with 1 M HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give the crude product (146 mg), which was purified by SiO<sub>2</sub> flash column chromatography (eluent 25–45% EtOAc/hexane) to give the phenolic carotene **1a** (84 mg, 0.16 mmol) in 72% yield as a red solid (*R*<sub>f</sub> = 0.40, 2:3 EtOAc/hexane). Data: <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 1.99 (s, 6H), 2.06 (s, 6H), 2.24 (s, 12H), 6.28 (d, *J* = 11.2 Hz, 2H), 6.29–6.39 (m, 2H), 6.37 (d, *J* = 16.4 Hz, 2H), 6.43 (d, *J* = 14.8 Hz, 2H), 6.54 (s, 4H), 6.60 (d, *J* = 16.4 Hz, 2H), 6.69–6.79 (m, 2H), 6.78 (dd, *J* = 14.8, 11.2 Hz, 2H), 8.11 (br s, 2H) ppm; <sup>13</sup>C NMR (acetone-d<sub>6</sub>) δ 12.7, 12.8, 21.4, 115.7, 126.0, 126.4, 129.2, 131.1, 132.7, 133.6, 136.6, 137.3, 138.1, 138.4, 138.5, 156.6 ppm; UV (DMSO, *c* = 1.40 × 10<sup>-6</sup>)

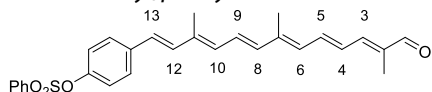
$\lambda_{\max}$  ( $\epsilon$ ) = 483 (369 197) nm; IR (KBr) 3356, 3032, 2916, 1736, 1597, 1466, 1373, 1304, 1204, 1150, 1026, 964, 910, 856, 733  $\text{cm}^{-1}$ ; HRMS (FAB) calcd for  $\text{C}_{38}\text{H}_{44}\text{O}_2$  532.3341, found 532.3343.

**Series II (b).** *(E)-4-(3-Oxobut-1-en-1-yl)phenyl Benzenesulfonate (5b)*. Yellow solid, 69% yield (5.73 g, 18.95 mmol) from 4-hydroxybenzaldehyde (**3b**). Data:  $R_f$  = 0.75 (hexane/acetone 1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.36 (s, 3H), 6.64 (d,  $J$  = 16.4 Hz, 1H), 7.02 (d,  $J$  = 8.4 Hz, 2H), 7.44 (d,  $J$  = 16.4 Hz, 1H), 7.47 (d,  $J$  = 8.4 Hz, 2H), 7.52–7.58 (m, 2H), 7.66–7.72 (m, 1H), 7.82–7.86 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 27.5, 122.8, 127.8, 128.3, 129.2, 129.4, 133.4, 134.4, 135.0, 141.4, 150.6, 197.9 ppm; IR (KBr) 1691, 1667, 1611, 1598, 1583, 1501, 1449, 1415, 1373, 1315, 1296, 1257, 1199, 1178, 1150, 1092, 1015, 977, 862, 829, 746, 694  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{14}\text{O}_4\text{S}+\text{Na}$  325.0505, found 325.0508.

*(E)-4-(3-Hydroxy-3-methylpenta-1,4-dien-1-yl)phenyl Benzenesulfonate*. Reddish-yellow oil. Data:  $R_f$  = 0.75 (hexane/acetone 1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45 (s, 3H), 5.10 (dd,  $J$  = 10.4, 0.8 Hz, 1H), 5.28 (dd,  $J$  = 17.2, 0.8 Hz, 1H), 6.00 (dd,  $J$  = 17.2, 10.4 Hz, 1H), 6.24 (d,  $J$  = 16.0 Hz, 1H), 6.54 (d,  $J$  = 16.0 Hz, 1H), 6.89 (d,  $J$  = 8.4 Hz, 2H), 7.26 (d,  $J$  = 8.4 Hz, 2H), 7.48–7.54 (m, 2H), 7.63–7.68 (m, 1H), 7.79–7.84 (m, 2H) ppm; IR (KBr) 3307, 2982, 1669, 1605, 1443, 1391, 1367, 1231, 1163, 1021, 961, 884, 813, 773 665  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_4\text{S}+\text{Na}$  353.0818, found 353.0822.

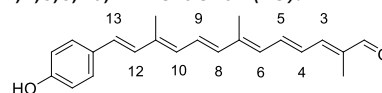
*((2E,4E)-3-Methyl-5-(4-((phenylsulfonyl)oxy)phenyl)-penta-2,4-dien-1-yl)triphenylphosphonium (6b)*. Yellow solid, 25% yield (3.32 g, 5.17 mmol,  $E/Z$  = 3:1 by  $^1\text{H}$  NMR). Data:  $R_f$  = 0.15 (MC/MeOH 1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.51 (dd,  $J$  = 4.0, 0.8 Hz, 3H), 4.82 (dd,  $J$  = 16.0, 8.0 Hz, 2H), 5.58 (q,  $J$  = 8.0 Hz, 1H), 6.44 (dd,  $J$  = 16.0, 2.8 Hz, 1H), 6.71 (dd,  $J$  = 16.0, 0.8 Hz, 1H), 7.18–7.23 (m, 1H), 7.25–7.31 (m, 2H), 7.35 (d,  $J$  = 8.0 Hz, 2H), 7.67–7.90 (m, 19H) ppm; IR (KBr) 1716, 1587, 1500, 1438, 1371, 1199, 1180, 1150, 1112, 1092, 1014, 997, 964, 912, 866, 798, 722, 687  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{36}\text{H}_{32}\text{O}_3\text{PS}$  575.1804, found 575.1840.

*4-((1E,3E,5E,7E,9E,11E)-3,7,12-Trimethyl-13-oxotrideca-1,3,5,7,9,11-hexaen-1-yl)phenyl Benzenesulfonate (8b)*.



Red solid (recrystallized from MeOH), 63% yield (438 mg, 0.95 mmol). Data:  $R_f$  = 0.25 (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.89 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 6.33 (d,  $J$  = 12.0 Hz, 2H; H-6, H-10), 6.43 (d,  $J$  = 14.8 Hz, 1H; H-8), 6.54 (d,  $J$  = 16.0 Hz, 1H; H-12), 6.70 (dd,  $J$  = 14.8, 12.0 Hz, 1H; H-5), 6.79 (dd,  $J$  = 14.8, 12.0 Hz, 1H; H-9), 6.81 (d,  $J$  = 16.0 Hz, 1H; H-13), 6.92 (d,  $J$  = 8.4 Hz, 2H), 6.96 (d,  $J$  = 12.0 Hz, 1H; H-3), 7.03 (dd,  $J$  = 14.8, 12.0 Hz, 1H; H-4), 7.32 (d,  $J$  = 8.4 Hz, 2H), 7.50–7.56 (m, 2H), 7.64–7.69 (m, 1H), 7.82–7.86 (m, 2H), 9.45 (s, 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.6, 12.9, 13.0, 29.6, 122.5, 126.6, 127.2, 127.3, 127.8, 128.4, 129.1, 131.7, 133.3, 134.2, 134.3, 135.3, 136.7, 136.8, 137.0, 137.5, 137.8, 141.4, 148.4, 148.7, 194.4 ppm; UV ( $\text{CHCl}_3$ ,  $c$  =  $1.93 \times 10^{-7}$ )  $\lambda_{\max}$  ( $\epsilon$ ) = 442 (2 439 421) nm; IR (KBr) 3018, 2838, 1666, 1605, 1540, 1510, 1357, 1247, 1214, 1174, 1006, 964, 833, 751, 689, 667  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{28}\text{H}_{28}\text{O}_4\text{S}+\text{Na}$  483.1601, found 483.1604.

*(2E,4E,6E,8E,10E,12E)-13-(4-Hydroxyphenyl)-2,7,11-trimethyltrideca-2,4,6,8,10,12-hexaenal (2b)*.



Dark red solid (triturated with  $\text{Et}_2\text{O}$ ), 96% yield (226 mg, 0.71 mmol, 1.7:1 all- $E:Z$ ). Data for all- $E$  isomer:  $R_f$  = 0.19 (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.89 (s, 3H), 2.06 (s, 6H), 4.92 (s, 1H), 6.31 (d,  $J$  = 11.6 Hz, 1H; H-10), 6.33 (d,  $J$  = 11.6 Hz, 1H; H-6), 6.42 (d,  $J$  = 14.8 Hz, 1H; H-8), 6.59 (d,  $J$  = 15.6 Hz, 1H; H-12), 6.70 (dd,  $J$  = 14.8, 11.6 Hz, 1H; H-5), 6.77 (d,  $J$  = 15.6 Hz, 1H; H-13), 6.80 (d,  $J$  = 8.4 Hz, 2H), 6.79–6.86 (m, 1H; H-9), 6.97 (d,  $J$  = 11.6 Hz, 1H; H-3), 7.04 (dd,  $J$  = 14.8, 11.6 Hz, 1H; H-4) 7.34 (d,  $J$  = 8.4 Hz, 2H), 9.46 (s, 1H) ppm;  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  10.3, 13.8, 13.9, 117.3, 129.4, 129.4, 129.5, 130.1, 131.1, 132.2, 133.0, 133.2, 138.4, 138.4, 139.2, 139.5, 143.3, 150.1, 159.0, 195.2 ppm; UV (DMSO,  $c$  =  $2.23 \times 10^{-6}$ )  $\lambda_{\max}$  ( $\epsilon$ ) = 465 (300 796) nm; IR (KBr) 3268, 3031, 2921, 1694, 1654, 1605, 1538, 1512, 1437, 1379, 1357, 1256, 1209, 1187, 1170, 1151, 1050, 1013, 960, 846, 816, 755, 691  $\text{cm}^{-1}$ ; HRMS (ESI)  $\text{C}_{22}\text{H}_{24}\text{O}_2+\text{Na}$  343.1669, found 343.1672.

*((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(4,1-phenylene) Dibenzenesulfonate (9b)*. Dark red solid (recrystallization from MeOH), 35% yield (550 mg, 0.89 mmol). Data:  $R_f$  = 0.20 (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.99 (s, 6H), 2.02 (s, 6H), 6.28–6.33 (m, 2H), 6.33 (d,  $J$  = 11.6 Hz, 2H), 6.42 (d,  $J$  = 14.8 Hz, 2H), 6.49 (d,  $J$  = 16.0 Hz, 2H), 6.66 (dd,  $J$  = 14.8, 11.6 Hz, 2H), 6.64–6.68 (m, 2H), 6.81 (d,  $J$  = 16.0 Hz, 2H), 6.91 (d,  $J$  = 8.8 Hz, 4H), 7.32 (d,  $J$  = 8.8 Hz, 4H), 7.50–7.56 (m, 4H), 7.64–7.70 (m, 2H), 7.82–7.86 (m, 4H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.8, 12.8, 122.6, 124.9, 125.7, 127.2, 128.5, 129.1, 130.4, 133.3, 133.9, 134.2, 134.7, 135.1, 135.3, 136.6, 137.0, 138.7, 148.3 ppm; UV ( $\text{CHCl}_3$ ,  $c$  =  $1.00 \times 10^{-6}$ )  $\lambda_{\max}$  ( $\epsilon$ ) = 487 (499 829) nm; IR (KBr) 2919, 2850, 1498, 1367, 1219, 1199, 1173, 1150, 1093, 962, 872, 833, 773, 753, 700, 684  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{46}\text{H}_{44}\text{O}_6\text{S}_2+\text{Na}$  779.2472, found 779.2475.

*4,4'-((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)diphenol (1b)*. Dark red solid (recrystallized from MeOH), 35% yield (75 mg, 0.16 mmol). Data:  $R_f$  = 0.10 (hexane/acetone 3:1);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.96 (s, 6H), 1.99 (s, 6H), 6.32–6.42 (m, 2H), 6.35 (d,  $J$  = 12.0 Hz, 2H), 6.42 (d,  $J$  = 14.4 Hz, 2H), 6.55 (d,  $J$  = 16.0 Hz, 2H), 6.68–6.78 (m, 2H), 6.70 (dd,  $J$  = 14.4, 12.0 Hz, 2H, calcd), 6.73 (d,  $J$  = 8.4 Hz, 4H), 6.81 (d,  $J$  = 16.0 Hz, 2H), 7.33 (d,  $J$  = 8.4 Hz, 4H), 9.53 (s, 2H) ppm;  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  13.9, 14.0, 116.8, 126.6, 126.7, 128.9, 129.8, 131.5, 131.6, 132.9, 134.0, 137.1, 137.6, 138.5, 158.3 ppm; UV (DMSO,  $c$  =  $2.10 \times 10^{-6}$ )  $\lambda_{\max}$  ( $\epsilon$ ) = 499 (309 910) nm; IR (KBr) 3263, 2923, 1654, 1603, 1582, 1538, 1512, 1438, 1360, 1211, 1187, 1170, 1156, 1104, 1012, 961, 832, 816, 772, 691  $\text{cm}^{-1}$ ; HRMS (FAB) calcd for  $\text{C}_{34}\text{H}_{36}\text{O}_2$  476.2715, found 476.2706.

**Series III (c).** *4-Formyl-2,6-dimethylphenyl Benzenesulfonate (4c)*. Light yellow oil, 98% yield (10.32 g, 35.55 mmol). Data:  $R_f$  = 0.55 (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.21 (s, 6H), 7.57 (s, 2H), 7.58–7.64 (m, 2H), 7.71–7.77 (m, 1H), 7.97–8.02 (m, 2H), 9.92 (d,  $J$  = 1.6 Hz, 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 127.9, 129.4, 130.5, 133.5, 134.3, 134.4, 136.9, 151.7, 191.2 ppm; IR (KBr) 1697, 1597, 1476, 1449,



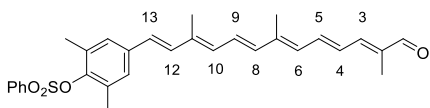
1371, 1303, 1194, 1167, 1116, 1088, 1036, 969, 949, 912, 876, 837, 752, 730, 710, 686  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{14}\text{O}_4\text{S}+\text{Na}$  313.0505, found 313.0509.

**(E)-2,6-Dimethyl-4-(3-oxobut-1-en-1-yl)phenyl Benzenesulfonate (5c).** Yellow solid, 88% yield (12.30 g, 37.23 mmol). Data:  $R_f = 0.30$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.14 (s, 6H), 2.36 (s, 3H), 6.64 (d,  $J = 16.0$  Hz, 1H), 7.22 (s, 2H), 7.40 (d,  $J = 16.0$  Hz, 1H), 7.56–7.62 (m, 2H), 7.69–7.77 (m, 1H), 7.96–8.01 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.2, 27.5, 127.5, 127.9, 129.0, 129.3, 132.7, 132.9, 134.2, 137.0, 142.0, 148.7, 198.1 ppm; IR (KBr) 2927, 1690, 1667, 1612, 1596, 1479, 1449, 1418, 1358, 1312, 1295, 1265, 1238, 1220, 1196, 1175, 1120, 1088, 1025, 976, 838, 772, 749, 729, 692  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_4\text{S}+\text{Na}$  353.0818, found 353.0820.

**(E)-4-(3-Hydroxy-3-methylpenta-1,4-dien-1-yl)-2,6-dimethylphenyl Benzenesulfonate.** Orange oil, Data:  $R_f = 0.32$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.47 (s, 3H), 2.10 (s, 6H), 5.12 (dd,  $J = 10.4, 1.2$  Hz, 1H), 5.30 (dd,  $J = 17.6, 1.2$  Hz, 1H), 6.02 (dd,  $J = 17.6, 10.4$  Hz, 1H), 6.24 (d,  $J = 16.0$  Hz, 1H), 6.50 (d,  $J = 16.0$  Hz, 1H), 7.04 (s, 2H), 7.55–7.60 (m, 2H), 7.67–7.73 (m, 1H), 7.96–8.00 (m, 2H) ppm; IR (KBr) 3421, 2974, 1598, 1479, 1449, 1369, 1219, 1196, 1175, 1119, 1089, 970, 915, 847, 772, 749, 730, 689  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}+\text{Na}$  381.1131, found 381.1134

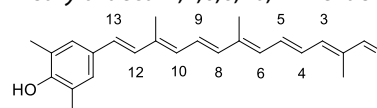
**((2E,4E)-5-(3,5-Dimethyl-4-((phenylsulfonyl)oxy)phenyl)-3-methylpenta-2,4-dien-1-yl)triphenylphosphonium Bromide (6c).** Yellow solid, 68% yield (5.35 g, 7.99 mmol, E:Z = 4:1). Data for E,E-isomer:  $R_f = 0.13$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (d,  $J = 4.0$  Hz, 3H), 2.07 (s, 6H), 4.85 (dd,  $J = 16.0, 8.0$  Hz, 2H), 5.59 (dt,  $J_d = 6.8, J_t = 8.0$  Hz, 1H), 6.33 (dd,  $J = 16.0, 2.0$  Hz, 1H), 6.64 (d,  $J = 16.0$  Hz, 1H), 7.03 (s, 2H), 7.55–7.97 (m, 20H) ppm; IR (KBr) 2919, 1703, 1587, 1480, 1438, 1367, 1219, 1196, 1176, 1112, 1088, 1027, 997, 963, 922, 846, 807, 771, 744, 730, 689  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{38}\text{H}_{36}\text{O}_3\text{PS}$  603.2117, found 603.2121.

**2,6-Dimethyl-4-((1E,3E,5E,7E,9E,11E)-3,7,12-trimethyl-13-oxotrideca-1,3,5,7,9,11-hexaen-1-yl)phenyl Benzenesulfonate (8c).**



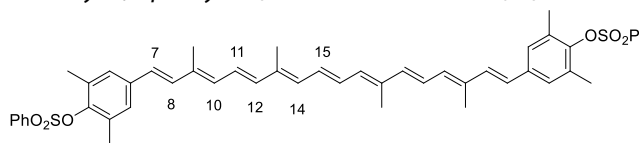
Red solid (recrystallization from ether), 21% yield (555 mg, 1.14 mmol). Data:  $R_f = 0.42$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.89 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.11 (s, 6H), 6.33 (d,  $J = 11.6$  Hz, 2H, H-6, H-10), 6.42 (d,  $J = 14.8$  Hz, 1H, H-8), 6.51 (d,  $J = 16$  Hz, 1H, H-12), 6.70 (dd,  $J = 14.0, 11.6$  Hz, 1H, H-5), 6.80 (dd,  $J = 14.8, 12.0$  Hz, 1H, H-9), 6.82 (d,  $J = 16.0$  Hz, 1H, H-13), 6.96 (d,  $J = 11.6$  Hz, 1H, H-3), 7.03 (dd,  $J = 14.0, 11.6$  Hz, 1H, H-4), 7.09 (s, 2H), 7.55–7.61 (m, 2H), 7.67–7.73 (m, 1H), 7.96–8.01 (m, 2H), 9.45 (s, 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.6, 12.9, 13.0, 17.3, 17.3, 127.1, 127.3, 127.7, 128.0, 129.2, 131.5, 132.3, 132.9, 133.9, 134.1, 136.0, 137.0, 137.1, 137.3, 137.5, 137.6, 141.5, 146.0, 146.7, 148.8, 194.4 ppm; UV ( $\text{CHCl}_3$ ,  $c = 8.26 \times 10^{-7}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 459 (899 101) nm; IR (KBr) 3032, 2919, 2862, 2815, 2711, 1659, 1609, 1585, 1540, 1477, 1448, 1406, 1354, 1311, 1271, 1198, 1174, 1106, 1088, 1007, 961, 844, 747, 733, 707, 687, 667  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{30}\text{H}_{32}\text{O}_4\text{S}+\text{Na}$  511.1914, found 511.1912.

**(2E,4E,6E,8E,10E,12E)-13-(4-Hydroxy-3,5-dimethylphenyl)-2,7,11-trimethyltrideca-2,4,6,8,10,12-hexaenal (2c).**



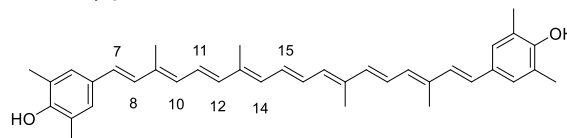
Dark red solid (recrystallization from ether), 19% yield (73 mg, 0.21 mmol). Data:  $R_f = 0.35$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.89 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.25 (s, 6H), 4.78 (br s, 1H), 6.30 (d,  $J = 11.2$  Hz, 1H, H-6), 6.32 (d,  $J = 11.2$  Hz, 1H, H-10), 6.40 (d,  $J = 14.8$  Hz, 1H, H-8), 6.54 (d,  $J = 16$  Hz, 1H, H-12), 6.69 (dd,  $J = 14.0, 11.2$  Hz, 1H, H-5), 6.76 (d,  $J = 16.0$  Hz, 1H, H-13), 6.82 (dd,  $J = 14.8, 11.2$  Hz, 1H, H-9), 6.97 (d,  $J = 11.2$  Hz, 1H, H-3), 7.04 (dd,  $J = 14.0, 11.2$  Hz, 1H, H-4), 7.09 (s, 2H), 9.45 (s, 1H) ppm; UV (DMSO,  $c = 2.29 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 465 (213 261) nm; IR (KBr) 3389, 2923, 2855, 1663, 1603, 1540, 1489, 1407, 1379, 1356, 1310, 1261, 1209, 1187, 1153, 1021, 963, 910, 800, 761, 735  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{28}\text{O}_2+\text{Na}$  371.1982, found 371.1991. The  $^{13}\text{C}$  NMR spectrum could not be obtained due to lower solubility of 2c in any solvent.

**((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(2,6-dimethyl-4,1-phenylene) Dibenzenesulfonate (9c).**



Dark red solid (recrystallization from MeOH), 37% yield (498 mg, 0.74 mmol). Data:  $R_f = 0.20$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.99 (s, 6H), 2.02 (s, 6H), 2.11 (s, 12H), 6.26–6.36 (m, 2H, H-14), 6.33 (d,  $J = 12.0$  Hz, 2H, H-10), 6.42 (d,  $J = 15.2$  Hz, 2H, H-12), 6.46 (d,  $J = 16.0$  Hz, 2H, H-8), 6.62–6.72 (m, 2H, H-15), 6.67 (dd,  $J = 15.2, 12.0$  Hz, 2H, H-11), 6.82 (d,  $J = 16.0$  Hz, 2H, H-7), 7.09 (s, 4H), 7.56–7.62 (m, 4H), 7.68–7.74 (m, 2H), 7.96–8.02 (m, 4H) ppm; UV ( $\text{CHCl}_3$ ,  $c = 2.11 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 487 (181 129) nm; IR (KBr) 3022, 2914, 2856, 1719, 1590, 1478, 1446, 1350, 1215, 1193, 1174, 1115, 1089, 964, 908, 851, 756, 733, 688, 669, 650  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{50}\text{H}_{52}\text{O}_6\text{S}_2+\text{Na}$  835.3098, found 835.3102.

**4,4'-((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(2,6-dimethylphenol) (1c).**



Dark red solid (recrystallization from MeOH), 67% yield (157 mg, 0.29 mmol). Data:  $R_f = 0.30$  (hexane/acetone 3:1);  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  2.05 (s, 6H), 2.06 (s, 6H), 2.23 (s, 12H), 6.30–6.38 (m, 2H, H-14), 6.34 (d,  $J = 11.2$  Hz, 2H, H-10), 6.43 (d,  $J = 14.8$  Hz, 2H, H-12), 6.55 (d,  $J = 16.0$  Hz, 2H, H-8), 6.73–6.80 (m, 4H, H-11, 15), 6.84 (d,  $J = 16.0$  Hz, 2H, H-7), 7.12 (s, 4H), 7.38 (s, 2H, -OH) ppm; UV (DMSO,  $c = 7.37 \times 10^{-7}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 501 (938 597) nm; IR (KBr) 3436, 3026, 2915, 1713, 1596, 1560, 1488, 1436, 1364, 1308, 1279, 1254, 1221, 1199, 1151, 1022, 957, 871, 836, 775, 723, 686  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{38}\text{H}_{44}\text{O}_2-\text{H}$  531.3258, found

531.3261. The  $^{13}\text{C}$  NMR spectrum could not be obtained due to lower solubility of **1c** in any solvent.

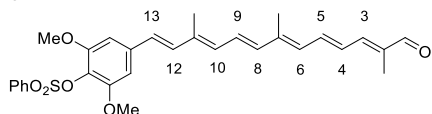
**Series IV (d). 4-Formyl-2,6-dimethoxyphenyl Benzenesulfonate (4d).** Ivory solid, 95% yield (9.42 g, 29.22 mmol). Data:  $R_f = 0.70$  (hexane/EtOAc 4:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.75 (s, 6H), 7.10 (s, 2H), 7.54–7.60 (m, 2H), 7.66–7.71 (m, 1H), 7.97–8.01 (m, 2H), 9.91 (s, 1H) ppm;  $^{13}\text{C}$  NMR  $\delta$  56.2, 106.0, 128.3, 128.7, 132.6, 133.8, 135.0, 137.6, 154.0, 190.8 ppm; IR (KBr) 1697, 1597, 1476, 1449, 1371, 1303, 1194, 1167, 1116, 1088, 969, 876, 837, 752, 730, 710, 686  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{14}\text{O}_4\text{S}+\text{Na}$  313.0505, found 313.0509.

**(E)-2,6-Dimethoxy-4-(3-oxobut-1-en-1-yl)phenyl Benzenesulfonate (5d).** Yellow solid, 87% yield (7.13 g, 19.67 mmol). Data:  $R_f = 0.61$  (hexane/acetone 1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.38 (s, 3H), 3.68 (s, 6H), 6.64 (d,  $J = 16.0$  Hz, 1H), 6.72 (s, 2H), 7.40 (d,  $J = 16.0$  Hz, 1H), 7.53–7.59 (m, 2H), 7.65–7.70 (m, 1H), 7.96–8.00 (m, 2H) ppm;  $^{13}\text{C}$  NMR  $\delta$  27.5, 55.9, 104.7, 127.9, 128.2, 128.6, 129.4, 133.6, 133.7, 137.6, 142.5, 153.5, 198.0 ppm; IR (KBr) 1670, 1613, 1593, 1499, 1450, 1420, 1372, 1346, 1244, 1220, 1179, 1131, 1092, 985, 855, 772, 733, 695  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_6\text{S}+\text{Na}$  385.0716, found 385.0718.

**(E)-4-(3-Hydroxy-3-methylpenta-1,4-dien-1-yl)-2,6-dimethoxyphenyl Benzenesulfonate.** Orange oil, Data:  $R_f = 0.64$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.47 (s, 3H), 3.63 (s, 6H), 5.12 (dd,  $J = 10.4, 1.2$  Hz, 1H), 5.30 (dd,  $J = 17.2, 1.2$  Hz, 1H), 6.02 (dd,  $J = 17.2, 10.4$  Hz, 1H), 6.26 (d,  $J = 16.0$  Hz, 1H), 6.52 (d,  $J = 16.0$  Hz, 1H), 6.55 (s, 2H), 7.50–7.56 (m, 2H), 7.61–7.67 (m, 1H), 7.93–7.98 (m, 2H) ppm; IR (KBr) 3009, 2939, 2849, 1670, 1612, 1593, 1499, 1450, 1420, 1371, 1346, 1321, 1244, 1220, 1179, 1130, 1092, 980, 855, 771, 733, 695  $\text{cm}^{-1}$ .

**((2E,4E)-5-(3,5-Dimethoxy-4-((phenylsulfonyl)oxy)phenyl)-3-methylpenta-2,4-dien-1-yl)triphenylphosphonium Bromide (6d).** Yellow solid, 57% yield (5.64 g, 8.04 mmol,  $E:Z = 5:1$ ). Data for  $E,E$ -isomer:  $R_f = 0.15$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  20:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.46 (d,  $J = 3.6$  Hz, 3H), 3.62 (s, 6H), 4.73 (dd,  $J = 16.0, 8.0$  Hz, 2H), 5.74 (dt,  $J_d = 7.2, J_t = 8.0$  Hz, 1H), 6.40 (dd,  $J = 16.0, 2.4$  Hz, 1H), 6.61 (s, 2H), 6.76 (d,  $J = 16.0$  Hz, 1H), 7.52–7.92 (m, 20H) ppm; IR (KBr) 1591, 1500, 1439, 1419, 1372, 1241, 1218, 1177, 1131, 1113, 1092, 907, 855, 723, 688  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{38}\text{H}_{36}\text{O}_5\text{PS}$  635.2016, found 635.2053.

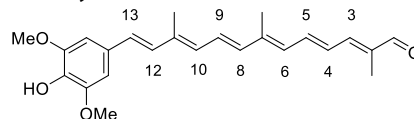
**2,6-Dimethoxy-4-((1E,3E,5E,7E,9E,11E)-3,7,12-trimethyl-13-oxotrideca-1,3,5,7,9,11-hexaen-1-yl)phenyl Benzenesulfonate (8d).**



Red solid (recrystallization from  $\text{Et}_2\text{O}$ ), 30% yield (370 mg, 0.71 mmol). Data:  $R_f = 0.16$  (hexane/acetone 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.87 (s, 3H), 2.02 (s, 6H), 3.65 (s, 6H), 6.30 (d,  $J = 11.6$  Hz, 1H, H-10), 6.36 (d,  $J = 11.6$  Hz, 1H, H-6), 6.40 (d,  $J = 14.8$  Hz, 1H, H-8), 6.51 (d,  $J = 16$  Hz, 1H, H-12), 6.60 (s, 2H), 6.68 (dd,  $J = 14.0, 11.6$  Hz, 1H, H-5), 6.78 (dd,  $J = 14.8, 11.6$  Hz, 1H, H-9), 6.82 (d,  $J = 16.0$  Hz, 1H, H-13), 6.95 (d,  $J = 12.0$  Hz, 1H, H-3), 7.01 (dd,  $J = 14.0, 12.0$  Hz, 1H, H-4), 7.49–7.57 (m, 2H), 7.62–7.68 (m, 1H), 7.94–8.01 (m, 2H), 9.43 (s, 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.6, 12.9, 13.0, 55.8, 55.8, 102.9, 127.3, 127.3, 127.6, 127.8, 128.3, 128.6, 131.7,

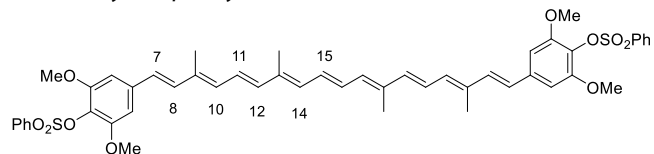
133.5, 133.6, 134.4, 136.8, 136.9, 137.2, 137.6, 137.8, 137.8, 141.5, 148.9, 153.3, 194.4 ppm; UV ( $\text{CHCl}_3$ ,  $c = 1.45 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 449 (386 736) nm; IR (KBr) 3007, 1656, 1586, 1541, 1500, 1449, 1417, 1370, 1351, 1274, 1243, 1182, 1129, 1091, 1006, 962, 909, 851, 751, 730, 710, 687, 667  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{30}\text{H}_{32}\text{O}_6\text{S}+\text{Na}$  543.1812, found 543.1814.

**(2E,4E,6E,8E,10E,12E)-13-(4-Hydroxy-3,5-dimethoxyphenyl)-2,7,11-trimethyltrideca-2,4,6,8,10,12-hexaenal (2d).**



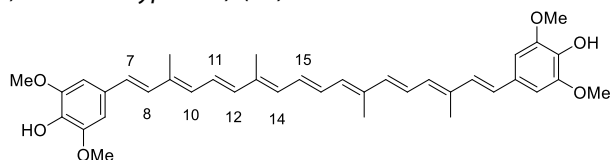
Dark red solid (recrystallization from  $\text{Et}_2\text{O}$ ), 45% yield (121 mg, 0.32 mmol). Data:  $R_f = 0.35$  (hexane/acetone 2:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.89 (s, 3H), 2.06 (s, 6H), 3.93 (s, 6H), 5.63 (br s, 1H), 6.32 (d,  $J = 12.0$  Hz, 1H, H-6), 6.34 (d,  $J = 11.2$  Hz, 1H, H-10), 6.41 (d,  $J = 14.8$  Hz, 1H, H-8), 6.56 (d,  $J = 16$  Hz, 1H, H-12), 6.69 (s, 2H), 6.69 (dd,  $J = 14.0, 12.0$  Hz, 1H, H-5), 6.77 (d,  $J = 16.0$  Hz, 1H, H-13), 6.82 (dd,  $J = 14.8, 11.2$  Hz, 1H, H-9), 6.96 (d,  $J = 11.6$  Hz, 1H, H-3), 7.03 (dd,  $J = 14.0, 11.6$  Hz, 1H, H-4), 9.45 (s, 1H) ppm;  $^{13}\text{C}$  NMR  $\delta$  9.6, 13.0, 13.0, 56.2, 56.2, 103.2, 127.5, 127.5, 128.6, 129.1, 131.2, 131.5, 131.9, 134.7, 136.9, 136.9, 137.3, 137.6, 141.6, 147.2, 148.9, 194.4 ppm; UV (DMSO,  $c = 2.06 \times 10^{-5}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 452 (19 006) nm; IR (KBr) 3034, 2921, 1655, 1603, 1540, 1514, 1456, 1423, 1338, 1218, 1186, 1157, 1114, 1010, 962, 772, 668  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{28}\text{O}_4+\text{Na}$  403.1880, found 403.1882.

**((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis(2,6-dimethoxy-4,1-phenylene) Dibzenesulfonate (9d).**



To a stirred solution of  $\text{C}_{20}$  bis(diethyl phosphonate) (0.12 g, 0.21 mmol) and 4-benzenesulfonyl-3,5-dimethoxybenzaldehyde (0.21 g, 0.63 mmol) in MeOH (5 mL) and toluene (5 mL) was added NaH (0.17 g, 4.2 mmol). The mixture was heated at 100  $^\circ\text{C}$  for 12 h under argon atmosphere. The crude mixture was quenched with 10%  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. The organic layer was separated, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give the crude red solid product, which was purified by recrystallization from MeOH/ $\text{Et}_2\text{O}$  to give carotene (48 mg, 0.010 mmol) in 26% yield as a dark red solid. Data:  $R_f = 0.34$  (2:1 hexane/acetone);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.99 (s, 6H), 2.03 (s, 6H), 3.68 (s, 12H), 6.25–6.36 (m, 2H, H-4), 6.36 (d,  $J = 12.0$  Hz, 2H, H-10), 6.43 (d,  $J = 14.8$  Hz, 2H, H-12), 6.47 (d,  $J = 16.0$  Hz, 2H, H-8), 6.60 (s, 4H), 6.63–6.68 (m, 2H, H-15), 6.66 (dd,  $J = 14.8, 12.0$  Hz, 2H, H-11), 6.82 (d,  $J = 16.0$  Hz, 2H, H-7), 7.52–7.58 (m, 4H), 7.63–7.68 (m, 2H), 7.97–8.02 (m, 4H) ppm;  $^{13}\text{C}$  NMR  $\delta$  12.8, 12.9, 55.9, 56.0, 102.8, 103.2, 126.7, 127.3, 128.3, 128.5, 130.4, 133.4, 133.5, 134.0, 134.7, 135.1, 136.7, 137.4, 137.9, 138.7, 153.3 ppm; UV ( $\text{CHCl}_3$ ,  $c = 1.61 \times 10^{-5}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 486 (32 953) nm; IR (KBr) 2920, 2844, 1585, 1498, 1449, 1417, 1374, 1347, 1242, 1175, 1230, 1114, 1092, 1008, 968, 962, 852, 771, 756, 730, 711, 687  $\text{cm}^{-1}$ ; HRMS (FAB) calcd for  $\text{C}_{50}\text{H}_{52}\text{O}_{10}\text{S}_2$  876.3002, found 876.3004.

4,4'-((1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-Tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaene-1,18-diyl)bis-(2,6-dimethoxyphenol) (**1d**).



Dark red solid (recrystallized from MeOH), 78% yield (183 mg, 0.31 mmol). Data:  $R_f = 0.20$  (hexane/acetone 2:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.00 (s, 6H), 2.04 (s, 6H), 3.93 (s, 12H), 6.25–6.34 (m, 2H, H-14), 6.33 (d,  $J = 10.8$  Hz, 2H, H-10), 6.41 (d,  $J = 14.4$  Hz, 2H, H-12), 6.51 (d,  $J = 16.0$  Hz, 2H, H-8), 6.64–6.73 (m, 2H, H-15), 6.68 (s, 4H), 6.69 (dd,  $J = 14.4$ , 10.8 Hz, 2H, H-11), 6.77 (d,  $J = 16.0$  Hz, 2H, H-7) ppm; UV (DMSO,  $c = 3.35 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 503 (184 559) nm; IR (KBr) 3536, 3498, 3029, 2841, 1703, 1601, 1554, 1514, 1456, 1425, 1401, 1338, 1307, 1290, 1262, 1217, 1155, 1114, 1010, 987, 962, 856, 833, 809, 705, 623  $\text{cm}^{-1}$ ; HRMS (FAB) calcd for  $\text{C}_{38}\text{H}_{44}\text{O}_6$  596.3138, found 596.3142. The  $^{13}\text{C NMR}$  spectrum could not be obtained due to lower solubility of **1d** in any solvent.

**Series V (e). Ethyl 5-Hydroxy-3-methyl-[1,1'-biphenyl]-2-carboxylate (3e).**<sup>17</sup> Yellow oil, 42% yield (4.28 g, 16.70 mmol). Data:  $R_f = 0.50$  (1:4 hexane/EtOAc);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.90 (t,  $J = 7.2$  Hz, 3H), 2.32 (s, 3H), 4.00 (q,  $J = 7.2$  Hz, 2H), 6.59 (d,  $J = 2.4$  Hz, 1H), 6.61 (d,  $J = 2.4$  Hz, 1H), 7.24–7.34 (m, 5H) ppm;  $^{13}\text{C NMR}$   $\delta$  13.5, 19.9, 61.1, 114.3, 116.1, 125.2, 127.3, 128.0, 128.1, 138.1, 140.9, 142.7, 156.6, 170.7 ppm; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{16}\text{O}_3 + \text{Na}$  279.0992, found 279.0996.

**6-(Hydroxymethyl)-5-methyl-[1,1'-biphenyl]-3-ol.** To a stirred solution of the above benzenecarboxylic ester **3e** (14.18 g, 55.34 mmol) in THF (20 mL) was added LAH (5.25 g, 138.35 mmol) at 0 °C. The mixture was heated at 90 °C for 20 min and cooled to room temperature. The mixture was quenched with 1 M HCl in ice-water, extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give the crude product, which was purified by flash column chromatography (hexane/EtOAc from 8:1 to 1:1) to afford benzylic alcohol (6.86 g, 32 mmol) in 58% yield as a white solid. Data:  $R_f = 0.21$  (4:1 hexane/EtOAc);  $^1\text{H NMR}$  (acetone- $d_6$ )  $\delta$  2.43 (s, 3H), 3.77 (br s, 1H), 4.42 (s, 2H), 6.58 (d,  $J = 2.4$  Hz, 1H), 6.71 (d,  $J = 2.4$  Hz, 1H), 7.30–7.35 (m, 1H), 7.35–7.40 (m, 2H), 7.42–7.46 (m, 2H), 8.32 (br s, 1H) ppm;  $^{13}\text{C NMR}$  (acetone- $d_6$ )  $\delta$  20.2, 59.8, 115.4, 117.9, 128.1, 129.2, 129.3, 130.6, 141.6, 143.3, 145.6, 157.5 ppm; IR (KBr) 3407, 3064, 1592, 1475, 1457, 1441, 1405, 1321, 1266, 1220, 1171, 1108, 1073, 1030, 1011, 972, 952, 855, 771, 717, 700  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_2 + \text{Na}$  237.0886, found 237.0888.

**5-Hydroxy-3-methyl-[1,1'-biphenyl]-2-carbaldehyde.** To a stirred solution of the above crude benzylic alcohol (9.0 g, 42 mmol) in acetone (40 mL) were added silica gel (11.0 g) and PCC (10.86 g, 50.4 mmol). The mixture was stirred at room temperature for 5 h under argon atmosphere and filtered through a sintered glass funnel under reduced pressure. The filter cake was rinsed with 200 mL of hexane/EtOAc (v:v = 2:1). The filtrate was washed with  $\text{NaHCO}_3$  solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give the crude product, which was purified by  $\text{SiO}_2$  flash column chromatography (hexane/acetone 7:1–7:3) to give titled

aldehyde (7.68 g, 36 mmol) in 86% as a light yellow solid. Data:  $R_f = 0.40$  (hexane/acetone = 7:3);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.64 (s, 3H), 6.54 (br s, 1H), 6.70 (d,  $J = 1.6$  Hz, 1H), 6.74 (d,  $J = 1.6$  Hz, 1H), 7.28–7.34 (m, 2H), 7.38–7.44 (m, 3H), 9.81 (s, 1H) ppm;  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  22.1, 115.3, 118.1, 125.8, 128.0, 128.2, 129.8, 138.7, 144.0, 151.0, 159.0, 193.5 ppm; IR (KBr) 3246, 1660, 1596, 1571, 1463, 1437, 1331, 1272, 1221, 1176, 1113, 866, 796, 771, 703, 662  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{12}\text{O}_2 + \text{Na}$  235.0730, found 235.0733.

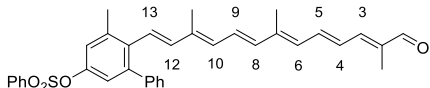
**6-Formyl-5-methyl-[1,1'-biphenyl]-3-yl Benzenesulfonate (4e).** Claybank oil, 95% yield (5.69 g, 16.15 mmol). Data:  $R_f = 0.70$  (hexane/EtOAc 4:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.58 (s, 3H), 6.91 (d,  $J = 3.2$  Hz, 1H), 6.95 (d,  $J = 3.2$  Hz, 1H), 7.18–7.24 (m, 2H), 7.39–7.45 (m, 3H), 7.55–7.60 (m, 2H), 7.69–7.74 (m, 1H), 7.88–7.94 (m, 2H), 9.86 (s, 1H) ppm;  $^{13}\text{C NMR}$   $\delta$  21.5, 121.9, 124.4, 128.5, 128.7, 129.3, 128.8, 131.3, 134.5, 137.4, 142.8, 148.9, 151.1, 193.2 ppm; IR (KBr) 1750, 1607, 1449, 1373, 1316, 1285, 1238, 1220, 1189, 1115, 1091, 1060, 1041, 1003, 985, 952, 889, 871, 806, 773, 739, 684  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{16}\text{O}_4\text{S} + \text{Na}$  375.0662, found 375.0665.

**(E)-5-Methyl-6-(3-oxobut-1-en-1-yl)-[1,1'-biphenyl]-3-yl Benzenesulfonate (5e).** White solid, 62% yield (6.31 g, 16.08 mmol). Data:  $R_f = 0.38$  (hexane/EtOAc 4:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.13 (s, 3H), 2.39 (s, 3H), 6.07 (d,  $J = 16.4$  Hz, 1H), 6.78 (d,  $J = 2.4$  Hz, 1H), 6.96 (d,  $J = 2.4$  Hz, 1H), 7.10–7.16 (m, 2H), 7.32–7.38 (m, 3H), 7.35 (d,  $J = 16.4$  Hz, 1H), 7.54–7.59 (m, 2H), 7.67–7.73 (m, 1H), 7.88–7.93 (m, 2H) ppm;  $^{13}\text{C NMR}$   $\delta$  21.5, 27.2, 121.6, 123.5, 127.8, 128.2, 128.4, 129.2, 129.5, 131.7, 133.6, 134.3, 135.4, 139.2, 139.7, 141.1, 144.1, 148.8, 198.1 ppm; IR (KBr) 3062, 1693, 1666, 1612, 1588, 1466, 1449, 1373, 1304, 1253, 1190, 1141, 1093, 974, 912, 884, 867, 820, 772, 753, 730, 716, 702, 686  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{20}\text{O}_4\text{S} + \text{Na}$  415.0975, found 415.0978.

**(E)-6-(3-Hydroxy-3-methylpenta-1,4-dien-1-yl)-5-methyl-[1,1'-biphenyl]-3-yl Benzenesulfonate.** Yellow oil. Data:  $R_f = 0.68$  (hexane/EtOAc = 4:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.19 (s, 3H), 2.29 (s, 3H), 4.97 (dd,  $J = 10.4$ , 1.2 Hz, 1H), 5.04 (dd,  $J = 17.6$ , 1.2 Hz, 1H), 5.42 (d,  $J = 16.4$  Hz, 1H), 5.79 (dd,  $J = 17.6$ , 10.4 Hz, 1H), 6.36 (d,  $J = 16.4$  Hz, 1H), 6.69 (d,  $J = 2.8$  Hz, 1H), 6.89 (d,  $J = 2.8$  Hz, 1H), 7.08–7.12 (m, 2H), 7.22–7.33 (m, 3H), 7.52–7.57 (m, 2H), 7.65–7.71 (m, 1H), 7.86–7.92 (m, 2H) ppm; IR (KBr) 3421, 3059, 2974, 2928, 1588, 1466, 1449, 1372, 1307, 1220, 1190, 1141, 1093, 974, 917, 883, 772, 751, 687  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{24}\text{O}_4\text{S} + \text{Na}$  443.1288, found 443.1291.

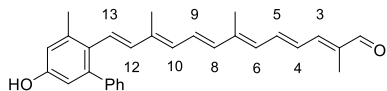
**((2E,4E)-3-Methyl-5-(3-methyl-5-(phenylsulfonyloxy)-[1,1'-biphenyl]-2-yl)penta-2,4-dien-1-yl)-triphenylphosphonium Bromide (6e).** Yellow solid, 68% yield (7.79 g, 10.65 mmol, E:Z = 4:1). Data for E,E-isomer:  $R_f = 0.15$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}=20:1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.24 (s, 3H), 2.25 (s, 3H), 4.77 (dd,  $J = 12.8$ , 8.0 Hz, 2H), 5.18 (dt,  $J_d = 6.4$ ,  $J_t = 8.0$  Hz, 1H), 5.85 (d,  $J = 16.0$  Hz, 1H), 6.21 (d,  $J = 16.0$  Hz, 1H), 6.62 (br s, 1H), 6.84 (br s, 1H), 7.02–7.09 (m, 2H), 7.09–7.16 (m, 1H), 7.17–7.26 (m, 2H), 7.52–7.92 (m, 20H) ppm; IR (KBr) 3055, 1586, 1437, 1369, 1306, 1220, 1189, 1140, 1111, 1092, 972, 882, 773, 749, 721, 687  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{43}\text{H}_{38}\text{O}_3\text{PS}$  665.2279, found 665.2283.

5-Methyl-6-((1E,3E,5E,7E,9E,11E)-3,7,12-trimethyl-13-oxotrideca-1,3,5,7,9,11-hexaen-1-yl)-[1,1'-biphenyl]-3-yl Benzenesulfonate (**8e**).



Red solid, 21% yield (288 mg, 0.52 mmol). Data:  $R_f = 0.32$  (hexane/acetone = 3:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.84 (s, 3H), 1.88 (s, 3H), 2.01 (s, 3H), 2.37 (s, 3H), 6.03 (d,  $J = 11.2$  Hz, 1H, H-6), 6.16 (d,  $J = 16.4$  Hz, 1H, H-12), 6.29 (d,  $J = 11.6$  Hz, 1H, H-10), 6.35 (d,  $J = 15.2$  Hz, 1H, H-8), 6.37 (d,  $J = 16.0$  Hz, 1H, H-13), 6.68 (dd,  $J = 14.8, 11.2$  Hz, 1H, H-5), 6.70 (d,  $J = 2.4$  Hz, 1H), 6.72 (dd,  $J = 15.2, 11.6$  Hz, 1H, H-9), 6.92 (d,  $J = 2.4$  Hz, 1H), 6.95 (d,  $J = 12.0$  Hz, 1H, H-3), 7.01 (dd,  $J = 14.8, 12.0$  Hz, 1H, H-4), 7.14–7.18 (m, 2H), 7.27–7.35 (m, 3H), 7.52–7.58 (m, 2H), 7.65–7.71 (m, 1H), 7.87–7.93 (m, 2H), 9.45 (s, 1H) ppm;  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.6, 12.6, 13.0, 21.6, 121.4, 123.2, 125.8, 127.1, 127.2, 127.6, 127.9, 128.5, 129.1, 129.6, 131.4, 132.2, 134.1, 134.8, 135.6, 137.0, 137.1, 137.4, 137.5, 138.2, 139.7, 140.7, 141.4, 142.8, 147.4, 148.8, 194.4 ppm; UV ( $\text{CHCl}_3$ ,  $c = 1.27 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 444 (419 628) nm; IR (KBr) 3032, 2918, 1660, 1609, 1594, 1544, 1465, 1448, 1407, 1374, 1355, 1304, 1211, 1188, 1141, 1093, 1006, 971, 884, 823, 752, 717, 702, 687, 667, 631  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{35}\text{H}_{34}\text{O}_4\text{S}+\text{Na}$  573.2070, found 573.2069.

(2E,4E,6E,8E,10E,12E)-13-(5-Hydroxy-3-methyl-[1,1'-biphenyl]-2-yl)-2,7,11-trimethyltrideca-2,4,6,8,10,12-hexaen-1-ol (**2e**).



Red powder, 13% yield (80 mg, 0.19 mmol). Data:  $R_f = 0.28$  (hexane/acetone = 3:1);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.85 (s, 3H), 1.88 (s, 3H), 2.02 (s, 3H), 2.41 (s, 3H), 5.46 (br s, 1H), 6.01 (d,  $J = 11.6$  Hz, 1H, H-6), 6.13 (d,  $J = 16.0$  Hz, 1H, H-12), 6.28 (d,  $J = 11.6$  Hz, 1H, H-10), 6.33 (d,  $J = 14.8$  Hz, 1H, H-8), 6.44 (d,  $J = 16.0$  Hz, 1H, H-13), 6.62 (d,  $J = 2.4$  Hz, 1H), 6.67 (dd,  $J = 14.8, 11.6$  Hz, 1H, H-5), 6.73 (d,  $J = 2.4$  Hz, 1H), 6.74 (dd,  $J = 14.8, 11.6$  Hz, 1H, H-9), 6.96 (d,  $J = 12.0$  Hz, 1H, H-3), 7.02 (dd,  $J = 14.8, 12.0$  Hz, 1H, H-4), 7.26–7.38 (m, 5H), 9.44 (s, 1H) ppm;  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.6, 12.7, 13.0, 21.8, 115.0, 116.8, 126.8, 127.1, 127.3, 127.6, 127.8, 128.0, 129.7, 129.7, 130.7, 130.9, 131.0, 136.6, 136.7, 137.9, 138.1, 141.9, 141.9, 143.2, 149.3, 154.2, 194.7 ppm; UV (DMSO,  $c = 2.66 \times 10^{-6}$ )  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 450 (164 286) nm; IR (KBr) 3310, 2921, 1655, 1595, 1541, 1465, 1407, 1356, 1318, 1260, 1210, 1183, 1010, 965, 907, 862, 754, 728, 701  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{29}\text{H}_{30}\text{O}_2+\text{Na}$  433.2138, found 433.2140.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c04432>.

$^1\text{H}/^{13}\text{C}$  NMR spectra, HPLC data for **9a**, **2b**, **1b**, and **1d**; graphs of DPPH and ABTS assay results; and DFT calculations for the energy levels of **2b** and **1b** (PDF)

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### Author Contributions

G.S. contributed to the synthesis (lead), DPPH and ABTS assays (lead), and DFT calculation (lead). L.G. performed synthesis (supporting) and investigation (supporting). H.J. performed synthesis (supporting) and investigation (supporting). W.-J.C. carried out data curation (supporting) and DFT calculation (supporting). S.K. contributed to data curation (lead), funding acquisition (lead), formal analysis (lead), investigation (lead), project administration (lead), synthesis (supporting), and manuscript writing (lead).

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### Notes

The authors declare no competing financial interest.

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## DEDICATION

†This paper is dedicated to my dear Professor Lanny S. Liebeskind.

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